IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: United States Patent No. RE37,721

Attn: Box Patent Ext.

Inventor: Stuart B. Rosenblum, et al.

Date of Reissued Patent: May 28,2002

Issue Date of U.S. Patent No. 5,767,115: June 16, 1998

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM

Sir:

Transmitted herewith for filing is an application for extension of term of U.S. Patent No. RE37,721 and two additional copies of the papers thereof.

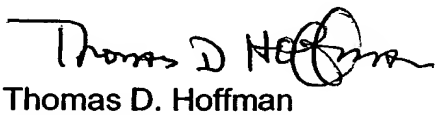
Also submitted herewith is an additional original declaration and power of attorney to prosecute the application requesting extension of U.S. Patent No. RE37,721. Therefore, the present application is complete.

Applicant, Schering Corporation ("Schering"), states that Schering is the owner of U.S. Patent No. RE37,721 as evidenced by the assignment to Schering Corporation (see Exhibit I), and that MSP Singapore Company, LLC is the holder of the regulatory approval granted with respect to the regulatory review period for ZETIA™ (ezetimibe) Tablets as evidenced by: (1) submission on February 28,1997 by Schering of IND # 52,791 to the Food and Drug Administration ("FDA") for the purpose of conducting clinical studies for the use of ezetimibe (SCH 58235) capsules for use in humans (see Exhibits II, III, IV & V); (2) the submission on December 27, 2001 by MSP Singapore Company, LLC of NDA # 21-445 (see

Exhibits VI & VII); and (3) the FDA letter dated October 25, 2002 approving NDA # 21-445 for use of (i) ZETIA™ (ezetimibe) Tablets administered alone as adjunctive therapy to diet for the reduction of elevated total cholesterol ("total-C"), low density lipoprotein cholesterol ("LDL-C"), and apolipoprotein B ("Apo B") in patients with primary (heterozygous familial and non-familial) hypercholesterolemia, (ii) ZETIA™ (ezetimibe)Tablets administered in combination with an HMG-CoA reductase inhibitor as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia, (iii) the combination of ZETIA™ (ezetimibe)Tablets and either atorvastatin or simvastatin in patients with homozygous familial hyper-cholesterolemia ("HoFH"), as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or, if such treatments are unavailable, in combination with either atorvastatin or simvastatin alone; and (iv) ZETIA™ (ezetimibe)Tablets as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia (see Exhibits VIII & IX).

The Commissioner is hereby authorized to charge payment in the amount of $ 1,120.00 and of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 19-0365. A duplicate copy of this sheet is enclosed.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re: United States Patent No. RE37,721 : Attn: Box Patent Ext.

Inventors: Stuart B. Rosenblum, et al. :

Date of Reissued Patent: May 28, 2002 :

Issue Date of U.S. Patent No. 5,767,115: June 16, 1998 :

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Washington, D.C. 20231

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

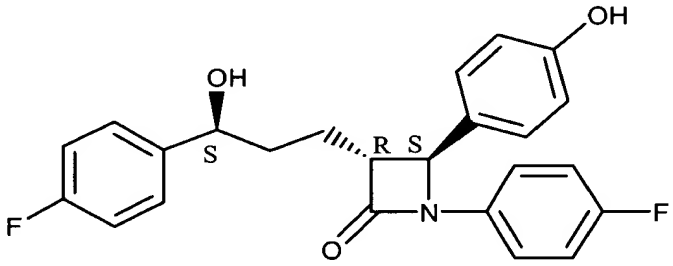
Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710 - 1.791, Schering Corporation ("Schering") hereby requests an extension of the patent term of U.S. Patent No. RE37,721 pursuant to 35 U.S.C. §154(c)(1). Schering is the owner of the above-identified patent by virtue of the assignment to Schering by Stuart B. Rosenblum, Sundeep Dugar, Duane A. Burnett, John W. Clader, and Brian A. McKittrick (executed on August 3, 1994) of their interests in International Patent Application No. PCT/US94/10099, filed on September 14, 1994, and U.S. Patent Application Serial No. 08/617,751, filed on March 18, 1996, which issued as U.S. Patent No. 5,767,115, and claiming priority to U.S. Patent Application Serial Nos. 08/102,440, filed September 21, 1993, and 08/257,593, filed June 9, 1994, said assignment being recorded in the United States Patent and Trademark Office ("USPTO") on May 20, 1996, at Reel 7960, Frame 0455 (copy attached hereto as Exhibit I).

The following information is submitted in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791, and follows the numerical format set forth in 37 C.F.R. §1.740:

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is ZETIA™ (ezetimibe) Tablets. As used herein, the United States Adopted Name ("USAN") for the active ingredient in the approved product is ezetimibe. As shown in Exhibit IX, the ZETIA™ Product Information Sheet, the active ingredient in the approved product has the following chemical structural formula, chemical name, molecular formula and physical properties.

Chemical Structural Formula:



USAN Name:	Ezetimibe
Code Name:	SCH 58235
CAS Number:	163222-33-1
Chemical Name:	1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-

2-azetidinone.

Molecular Formula:	$C_{24}H_{21}F_2NO_3$
Molecular Weight:	409.4
Physical Form:	White crystalline powder
Chirality:	Ezetimibe has three chiral centers.

(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

The regulatory review for ZETIA® (ezetimibe) Tablets occurred under Section 505 of the Federal, Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §355. See Exhibit VIII. Section 505 of the FFDCA provides for the submission and approval of a new drug as defined in 21 U.S.C. §321(p).

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

ZETIA™ (ezetimibe) Tablets were approved by the Food and Drug Administration ("FDA") for commercial marketing and use on October 25, 2002. See Exhibit VIII.

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, THE PUBLIC

HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT, OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED:

The active ingredient in the approved product, ZETIA™ (ezetimibe) Tablets, has the USAN name of ezetimibe and the chemical name listed in Paragraph No. (1) hereinabove as well as in the upper left hand paragraph of page 1 of Exhibit IX, the ZETIA™ Product Information Sheet. The active ingredient, ezetimibe, approved for marketing and use under Section 505 of the FFDCA, has not previously been approved for commercial marketing or use under the FFDCA, The Public Health Service Act or the Virus-Serum-Toxin Act. As identified in Exhibit VIII, the active ingredient, ezetimibe, was approved for the following indications:

- primary hypercholesterolemia (as monotherapy and in combination with HMG-CoA reductase inhibitors);
- homozygous familial hypercholesterolemia(in combination with either atorvastatin or simvastatin); and
- homozygous familial sitosterolemia.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SEC. 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

The product was approved on October 25, 2002, and the last day within the sixty-day period permitted for submission of an application for

extension of U.S. Patent No. RE37,721 is December 23, 2002. See Exhibit VIII. This application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. §1.720(f).

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION:

United States Patent No.:	RE37,721
Inventors:	Stuart B. Rosenblum, Sundeep Dugar, Duane A. Burnett, John W. Clader, and Brian A McKittrick
Date of Reissued Patent:	May 28, 2002
Expiration Date:	June 16, 2015
Date of Issue of U.S. Patent No. 5,767,115:	June 16, 1998
Expiration Date:	June 16, 2015

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS:

U.S. Patent No. 5,767,115 has been re-issued as U.S. Patent No. RE37,721. A copy of U.S. Patent No. RE37,721 is attached as Exhibit X.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR REEXAMINATION CERTIFICATE ISSUED IN THE PATENT:

No disclaimers have been filed for U.S. Patent No. RE37,721.

A certificate of correction has been issued for U.S. Patent No. 5,767,115, and is attached as Exhibit XI.

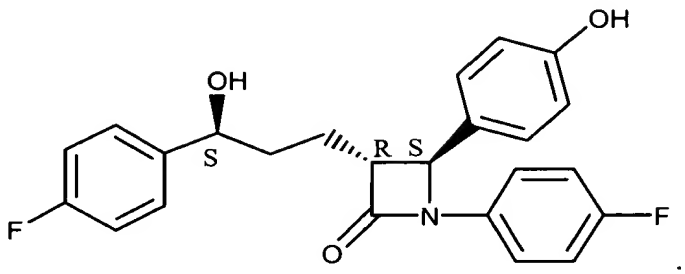
A certificate of correction has been issued for U.S. Patent No. RE37,721, and is attached as Exhibit XII.

The first maintenance fee for U.S. Patent No. 5,767,115 (RE37,721) was paid as shown by USPTO Maintenance Fee Statement from the USPTO website. See Exhibit XIII. Pursuant to 37 C.F.R. §1.362(h), the next maintenance fee for U.S. Patent No. RE37,721 is due (without surcharge) on December 19, 2005.

(9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

U.S. Patent No. RE37,721 claims the FDA approved product ZETIA™(ezetimibe)Tablets as the compound ezetimibe, pharmaceutical compositions containing ezetimibe, and methods of using ezetimibe. The structural formula of ezetimibe is shown in the upper left hand paragraph

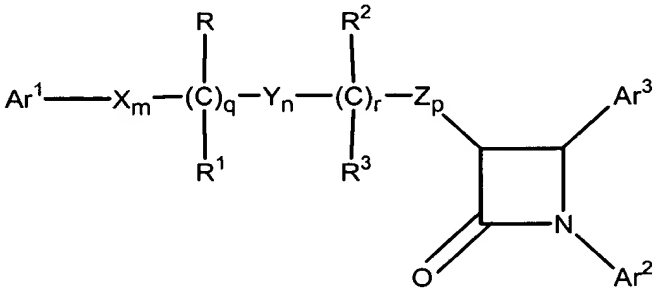
entitled **"DESCRIPTION"** on page 1 of Exhibit IX, the ZETIA™ Product Information Sheet, as follows:



At least claims 1, 2, 3, 5, and 7-13 of U.S. Patent No. RE37,721 read on the FDA approved product ZETIA™ (ezetimibe) Tablets for the approved indications. See Exhibit IX, the ZETIA™ Product Information Sheet, page 2, top right hand paragraph entitled **"INDICATIONS AND USAGE,"** and Exhibit VIII, page 1, third paragraph. See also U.S. Patent No. RE37,721, e.g., column 3, line 44 to column 4, line 12.

Claim 1 of U.S. Patent No. RE37,721 is:

1. A compound represented by the formula



or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of -CH_2-, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of -OR^6, -$O(CO)R^6$, -$O(CO)OR^9$ and -$O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR^6, -$O(CO)R^6$, -$O(CO)OR^9$, -$O(CH_2)_{1-5}OR^6$, -$O(CO)NR^6R^7$, -NR^6R^7, -$NR^6(CO)R^7$, -$NR^6(CO)OR^9$, -$NR^6(CO)NR^7R^8$, -$NR^6SO_2R^9$, -$COOR^6$, -$CONR^6R^7$, -COR^6, -$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, -$O(CH_2)_{1-10}$-$COOR^6$, -$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, -CH=CH-$COOR^6$, -CF_3, -CN, -NO_2 and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of -OR^6, -$O(CO)R^6$, -$O(CO)OR^9$, -$O(CH_2)_{1-5}OR^6$, -$(CO)NR^6R^7$, -NR^6R^7, -$NR^6(CO)R^7$, -$NR^6(CO)OR^9$, -$NR^6(CO)NR^7R^8$, -$NR^6SO_2R^9$, -$COOR^6$, -$CONR^6R^7$, -COR^6, -$SO_2NR^6R^7$, $S(O)_{0-2}R^9$, -$O(CH_2)_{1-10}$-$COOR^6$, -$O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and -CH=CH-$COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl.

The compound represented by the formula in claim 1 of U.S. Patent No. RE37,721 reads on ezetimibe wherein:

Ar^1 and Ar^2 are R^4-substituted aryl and R^4 is halogen (i.e., F);

Ar^3 is R^5-substituted phenyl and R^5 is OR^6 and R^6 is hydrogen;

R is $-OR^6$, and R^6 is hydrogen and R^1 is hydrogen and q is 1;

Y is $-CH_2-$ and n is 2; and

m and r and p are each 0.

Alternatively, the compound represented by the formula in claim 1 of U.S. Patent No. RE37,721 reads on ezetimibe wherein:

Ar^1 and Ar^2 are R^4-substituted aryl and R^4 is halogen (i.e., F);

Ar^3 is R^5-substituted phenyl and R^5 is OR^6 and R^6 is hydrogen;

R is $-OR^6$, and R^6 is hydrogen and R^1 is hydrogen and q is 1;

Z is $-CH_2-$ and p is 2; and

m and n and r are each 0.

See paragraph (1) hereinabove and the upper left hand paragraph on page 1 of Exhibit IX, the ZETIA™ Product Information Sheet, where the chemical structural formula of ezetimibe, the active ingredient in the approved product ZETIA™ (ezetimibe)Tablets is set forth.

Claim 2 of U.S. Patent No. RE37,721 is:

2. A compound of claim 1 wherein Ar^1 is phenyl or R^4-substituted phenyl, Ar^2 is phenyl or R^4-substituted phenyl and Ar^3 is R^5-substituted phenyl.

The compound of claim 2 of U.S. Patent No. RE37,721 reads on ezetimibe wherein:

Ar^1 is R^4-substituted phenyl wherein R^4 is halogen (i.e., F);

Ar^2 is R^4-substituted phenyl wherein R^4 is halogen (i.e., F); and

Ar^3 is R^5-substituted phenyl wherein R^5 is $-OR^6$ and R^6 is hydrogen, and wherein each of X, Z, R, R^1, R^2, R^3, m, n, p, and r has the same definition as that in the discussion regarding claim 1 reading on ezetimibe.

See paragraph (1) hereinabove and the upper left hand paragraph on page 1 of Exhibit IX, the ZETIA™ Product Information Sheet.

Claim 3 of U.S. Patent No. RE37,721 is:

3. A compound of claim 2 wherein Ar^1 is R^4-substituted phenyl wherein R^4 is halogen; Ar^2 is R^4-substituted phenyl wherein R^4 is halogen or $-OR^6$, wherein R^6 is lower alkyl or hydrogen; and Ar^3 is R^5-substituted phenyl, wherein R^5 is $-OR^6$, wherein R^6 is lower alkyl or hydrogen.

The compound of claim 3 of U.S. Patent No. RE37,721 reads on ezetimibe wherein:

Ar^1 is R^4- substituted phenyl wherein R^4 is halogen (i.e., F);

Ar^2 is R^4-substituted phenyl wherein R^4 is halogen (i.e., F); and

Ar^3 is R^5-substituted phenyl wherein R^5 is $-OR^6$ and R^6 is hydrogen, and wherein each of X, Z, R, R^1, R^2, R^3, m, n, p, and r has the same definition as that in the above discussion regarding claim 1 reading on ezetimibe.

See paragraph (1) hereinabove and the upper left hand paragraph on page 1 of Exhibit IX, the ZETIA™ Product Information Sheet.

Claim 5 of U.S. Patent No. RE37,721 is:

5. A compound of claim 1 wherein m, n and r are each zero, q is 1 and p is 2.

The compound of claim 5 of U.S. Patent No. RE37,721 reads on ezetimibe wherein:

m, n and r are each 0

q is 1; and

p is 2 ; and wherein

Ar^1 and Ar^2 are R^4-substituted aryl and R^4 is halogen (i.e., F);

Ar^3 is R^5-substituted phenyl and R^5 is OR^6 and R^6 is hydrogen;

R is $-OR^6$, and R^6 is hydrogen and R^1 is hydrogen and;

Z is $-CH_2-$.

See paragraph (1) hereinabove and the upper left hand paragraph on page 1 of Exhibit IX, the ZETIA™ Product Information Sheet.

Claim 7 of U.S. Patent No. RE37,721 is:

7. A compound selected from the group consisting of

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(R)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel 3(R)-(2(R)-hydroxy-2-phenylethyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(S)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(S)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(1(R)-hydroxy-3-phenylpropyl)-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

rel-3(R)-[(S)-hydroxy-(2-naphthalenyl)methyl]-4(S)-(4-methoxyphenyl)-1-phenyl)-1-phenyl-2-azetidinone;

rel-3(R)-[(R)-hydroxy-(2-naphthalenyl)methyl]-4(S)-(4-methoxyphenyl)-1-phenyl-2-azetidinone;

3(R)-(3(R)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl-2-azetidinone;

3(R)-(3(S)-hydroxy-3-phenylpropyl)-1,4(S)-bis-(4-methoxyphenyl-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-(4-hydroxyphenyl)-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

rel 3(R)-[3(RS)-hydroxy-3-[4-(methoxymethoxy)-phenyl]propyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(R)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone;

1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone;

3(R)-[3(R)-acetyloxy)-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(S)-acetyloxy)-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)-phenyl]-1-(4-fluorophenyl)-2-azetidinone;

3(R)-[3(R)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone;

3(R)-[3(S)-(acetyloxy)-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and

rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(1R)-(1(R)-hydroxy-3-phenylpropyl)-2-azetidinone.

The compound of claim 7 of U.S. Patent No.RE37,721 reads on ezetimibe wherein the compound recited in claim 7 is 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-

azetidinone. See paragraph (1) hereinabove after **"Chemical Name,"** and the second sentence in the top left hand paragraph, entitled **"DESCRIPTION"** on page 1 of Exhibit IX, the ZETIA™ Product Information Sheet, that lists a chemical name of ezetimibe that represents the same compound named in claim 7.

Claim 8 of U.S. Patent No. RE37,721 is

8. A pharmaceutical composition for the treatment or prevention of [athersclerosis], *atherosclerosis* or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

Claim 8 reads on ZETIA™ (ezetimibe)Tablets, the approved product, in that the ZETIA™ Tablet formulation contains the lipid-lowering compound, ezetimibe, that reduces blood cholesterol by selectively inhibiting the intestinal absorption of cholesterol and related phytosterols and that has the structural formula of a compound of claim 1. See Exhibit IX, the ZETIA™Product Information Sheet, on page 1, the upper left hand paragraph below the structural formula of ezetimibe, on page 1, the third upper left hand paragraph below **"CLINICAL PHARMACOLOGY,"** entitled **"Mode of Action,"** and the upper right hand paragraph on page 2, entitled **"INDICATIONS AND USAGE."**

Claim 9 of U.S. Patent No. RE37,721 is:

9. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 1.

Claim 9 reads on an approved method of ZETIA™ (ezetimibe)Tablets, the approved product, in that the ZETIA™ Tablet formulation contains the lipid-lowering compound, ezetimibe, that has been approved for use as monotherapy and in combination with other compounds, as adjunctive

therapy to reduce elevated total cholesterol, LDL-cholesterol , Apo-B , sitosterol and campesterol levels in patients and has the structural formula of a compound of claim 1; and exhibits the approved indications of reducing plasma cholesterol. See Exhibit IX, the ZETIA™ Product Information Sheet, page 1, the paragraph below the structural formula of ezetimibe, and the paragraph in the upper right hand column of page 2, entitled**" INDICATIONS AND USAGES ."**

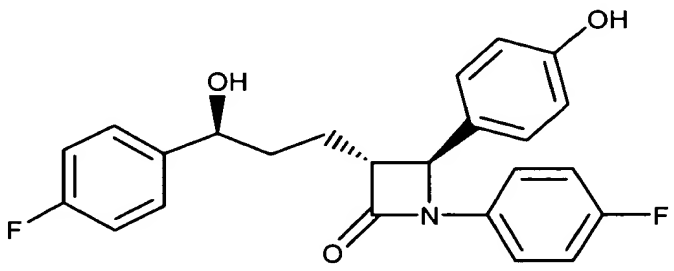
Claim 10 of U.S. Patent No. RE37,721 is:

10. *A compound comprising 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone or a pharmaceutically acceptable salt thereof.*

Claim 10 of U.S. Patent No. RE37,721 reads on ZETIA™(ezetimibe) Tablets, the approved product in that the compound recited in claim 10 is 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone. See paragraph (1) hereinabove after **"Chemical Name,"** and the second sentence in the top left hand paragraph, entitled **"DESCRIPTION"** on page 1 of Exhibit IX, the ZETIA™ Product Information Sheet, that lists a chemical name of ezetimibe that represents the same compound named in claim 10.

Claim 11 of U.S. Patent No. RE37,721 is:

11. A compound represented by the formula:



Claim 11 reads on ZETIA™(ezetimibe) Tablets, the approved product, in that claim 11 is the structural formula of ezetimibe. See paragraph (1), hereinabove and Exhibit IX, page 1 upper left hand paragraph entitled **'DESCRIPTION."**

Claim 12 of U.S. Patent No. RE37,721 is:

12. *A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound of claim 10 or 11 in a pharmaceutically acceptable carrier.*

Claim 12 reads on ZETIA™(ezetimibe) Tablets, the approved product, in that the ZETIA™Tablet formulation contains the lipid-lowering compound, ezetimibe, that has been approved for use as monotherapy and in combination with other compounds, as adjunctive therapy to reduce elevated total cholesterol, LDL-cholesterol , Apo-B , sitosterol and campesterol levels in patients and that has the structural formula of claim 10 and of claim 11. See Exhibit IX, the ZETIA™Product Information Sheet, page 1, the paragraph below the structural formula of ezetimibe, and the upper right hand paragraph on page 2, entitled **"INDICATIONS AND USAGE."**

Claim 13 of U.S. Patent No. RE37,721 is:

13. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound according to claims 10 or 11.

Claim 13 reads on the approved method of using ZETIA™ (ezetimibe)Tablets, the approved product, in that the ZETIA™Tablet formulation contains the lipid-lowering compound, ezetimibe, that has been approved for use as monotherapy and in combination with other compounds as adjunctive therapy, to reduce elevated total cholesterol, LDL-cholesterol ,

Apo-B , sitosterol and campesterol levels in patients; has the structural formula of claim 10 and of claim 11; and exhibits the approved indications of reducing plasma cholesterol. See Exhibit IX, the ZETIA™ Product Information Sheet, at the paragraph below the structural formula of ezetimibe in the upper left hand column of page 1, and the in the upper right hand column of page 2 entitled **"INDICATIONS AND USAGES."**

(10) A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG (IND) APPLICATION AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER; AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

IND Number: 52,791

IND Effective Date: May 23, 1997

NDA Number: 21-445

NDA Initial Submission Date: December 27, 2001

FDA Receipt of NDA Date: December 27, 2001

FDA Approval of NDA Date: October 25, 2002

Schering is the assignee of record of U.S. Patent No. RE37,721 by virtue of the assignment to Schering by Stuart B. Rosenblum, Sundeep Dugar, Duane A. Burnett, John W. Clader, and Brian A. McKittrick. See pages 1 and 2 hereinabove and Exhibit I.

On February 28, 1997, Schering submitted to the FDA an Investigational New Drug ("IND") Application for ezetimibe (SCH 58235)

capsules under Section 505 of the FFDCA for the purpose of conducting clinical studies to support the approval of a subsequent New Drug Application ("NDA") for the use of ZETIA™ (ezetimibe) Tablets to treat primary hypercholesterolemia in humans. A copy of this letter from Schering transmitting the IND application is attached as Exhibit II. By a letter dated March 6, 1997, the FDA acknowledged its receipt of the IND application on March 4, 1997 and assigned it IND # 52,791. A copy of this letter is attached as Exhibit III.

By a letter dated April 4, 1997, the FDA placed IND # 52,791 on clinical hold and requested certain information. A copy of this letter is attached as Exhibit IV. In a letter dated April 22, 1997, Schering responded to the FDA's April 4, 1997 letter and provided the requested information. A copy of this letter is also attached at Exhibit IV. In a letter dated May 23, 1997, the FDA acknowledged receipt of the Schering April 22, 1997 letter and lifted the clinical hold. A copy of this letter is attached as Exhibit V. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i) as May 23, 1997, the effective date the FDA lifted the clinical hold on IND # 52,791.

On December 27, 2001, MSP Singapore Co., LLC, a joint venture of Merck & Co., Inc., and Schering, submitted to the FDA an original NDA for ZETIA™(ezetimibe)Tablets under Section 505 of the FFDCA for treatment of:

- Primary hypercholesterolemia (heterozygous familial and non-familial), when administered alone or with an HMG-CoA reductase inhibitor, as an adjunct to diet and exercise;
- Hypercholesterolemia in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable, and

- Elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

A copy of this letter from MSP Singapore Co., LLC., transmitting the NDA is attached as Exhibit VI. The FDA received the NDA on December 27, 2001 and assigned it number NDA # 21-445 See Exhibit VII. This establishes December 27, 2001 as the end of the "testing phase" under IND # 52,791 of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(i) and the beginning of the "approval phase" under NDA # 21-445 of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(ii).

On October 25, 2002, the FDA approved NDA # 21-445 for the use of ZETIA™(ezetimibe)Tablets (10mg) for the following indications:

Primary hypercholesterolemia – as adjunctive therapy to diet for reduction of elevated total-C, LDL-C and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia either alone or with an HMG-Co A reductase inhibitor.

Homozygous familial hypercholesterolemia – in combination with either atorvastatin or simvastatin, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or, if such treatmentas are unavailable, in combination with either atorvastatin or simvastatin alone; and

Homozygous familial sitosterolemia – as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels.

A copy of the FDA approval letter is attached as Exhibit VIII. This establishes the end of the "regulatory review period" under 35 U.S.C. §156(g)(1)(B)(ii) as October 25, 2002.

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY SCHERING, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

During the applicable regulatory review period, Schering and MSP Singapore Co. LLC were actively involved in obtaining FDA approval for the use of ZETIA™(ezetimibe)Tablets .

As previously noted, Schering submitted an IND application on February 28, 1997 for ezetimibe. By letter dated March 6, 1997, the FDA acknowledged receipt of the IND application on March 4, 1997 and assigned it IND # 52,791. In the letter dated April 4,1997, the FDA further informed Schering that ZETIA™ (ezetimibe) studies were placed on clinical hold and requested further information. In a letter dated April 22, 1997, Schering provided to the FDA the information needed to resolve the clinical hold issues. In a letter dated May 23, 1997, the FDA lifted the clinical hold. During the period from May 23, 1997 through December 27, 2001, Schering, in close consultation with the FDA, conducted clinical trials under IND # 52,791.

On December 27, 2001, MSP Singapore Co., LLC, submitted an NDA for use of ZETIA™(ezetimibe)Tablets in humans as specified in the NDA.

The FDA received this NDA on December 27, 2001 and assigned it NDA # 21-445. From December 27, 2001 to October 25, 2002, MSP Singapore Co., LLC, interacted with various FDA officials and answered numerous questions, generated requested data and supplied requested information regarding all

clinical studies and data on the use of ZETIA™ (ezetimibe) Tablets (10mg) for treatment of:

- Primary hypercholesterolemia (heterozygous familial and non-familial), when administered alone or with an HMG-CoA reductase inhibitor, as an adjunct to diet and exercise;
- Hypercholesterolemia in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable, and
- Elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Schering acted with due diligence under IND # 52,791 during the "testing phase" of the regulatory review period under 35 U.S.C. §156(g)(1)(B)(i), i.e., from May 23, 1997 to December 27, 2001. Clinical studies that occurred during the "testing phase" of the regulatory review period under IND # 52,791 include those listed in the following table.

Number of Subjects	Brief Description of Study
124	Pilot dose ranging study of the safety and efficacy of ezetimibe tablets compared to placebo and to lovastatin in patients with primary hypercholesterolemia
243	Phase II Double-Blind Dose-Response. Study of the efficacy and safety for four doses of ezetimibe compared with placebo in subjects with primary hypercholesterolemia
189	Double-blind study of the efficacy and safety of morning versus evening doses of ezetimibe tablets compared to placebo in subjects with primary hypercholesterolemia
827	Phase III double-blind efficacy and safety study of ezetimibe tablets 10mg compared with placebo in subjects with primary hypercholesterolemia
892	Phase III double-blind efficacy and safety study of ezetimibe tablets 10mg compared with placebo in subjects with primary hypercholesterolemia
548	Phase III double-blind efficacy and safety study of ezetimibe tablets 10mg co-administered with lovastatin in subjects with primary hypercholesterolemia
688	Phase III double-blind efficacy and safety study of ezetimibe tablets 10mg co-administered with simvastatin in subjects with primary hypercholesterolemia
538	Phase III double-blind efficacy and safety study of ezetimibe tablets 10mg co-administered with pravastatin in subjects with primary hypercholesterolemia
628	Phase III double-blind efficacy and safety study of ezetimibe tablets 10mg co-administered with atorvastatin in subjects with primary hypercholesterolemia
769	A multicenter double-blind randomized, placebo-controlled study to evaluate the lipid-altering efficacy, safety and tolerability of ezetimibe when added to ongoing therapy with an HMG-COA reductase inhibitor (statin) in subjects with primary hypercholesterolemia, know coronary heart disease ("CHD") or multiple cardiovascular ("CV") risk factor"
50	A Phase III efficacy and safety study of ezetimibe tablets, 10 mg, co-administered with atorvastatin or simvastatin to treat subjects with homozygous familiar hypercholesterolemia
37	A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of ezetimibe tablets, 10 mg, with or without concomitant bile acid binding resin or other lipid-lowering therapy in subjects with homozygous sitosterolemia and absorption/turnover sub-study

Exhibit XIV identifies correspondence and communications between Schering and FDA officials concerning IND # 52,791, briefly describes significant and other activities by Schering during the "testing phase," and confirms that Schering acted with due diligence during this phase.

MSP Singapore Co., LLC, also acted with due diligence under NDA # 21-445 during the "approval phase" of the regulatory review period under 35 U.S.C. §156(g)(1)(B)(ii), i.e., from December 27, 2001 to October 25, 2002. Exhibit XV identifies correspondence and communications between MSP Singapore Co., LLC, and FDA officials concerning NDA # 21-445, briefly describes significant and other activities by MSP Singapore Co., LLC, during the "approval phase," and confirms that MSP Singapore Co., LLC, acted with due diligence during this phase.

Schering does not believe that copies of any of the correspondence or communications identified in Exhibits XIV and XV are required to be submitted pursuant to 37 C.F.R. §1.765. Copies of any or all of the correspondence and communications identified in those exhibits, or of the clinical studies identified above, will be provided to the USPTO upon its request.

Schering reserves the right to present additional information in support of the conclusion that it and MSP Singapore Co., LLC, acted with due diligence during the regulatory review period. See, e.g., 21 C.F.R. §60.32.

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 U.S.C. §154(c)(1), as amended (effective June 8, 1995) by the Uruguay Round Agreements Act, Pub. L. 103-465, 108 Stat. 4809 (1994), and 35 U.S.C. §156, the term of U.S. Patent No. RE37,721

currently expires on June 16, 2015. This patent term extension application is, therefore, being submitted prior to the expiration of the term of U.S. Patent No. RE37,721.

(2) The term of U.S. Patent No. RE37,721 has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Schering, the owner of record of United States Patent No. RE37,721. Schering is the owner of record by virtue of the assignment to Schering by Stuart B. Rosenblum, Sundeep Dugar, Duane A. Burnett, John W. Clader and Brian A. McKittrick. See pages 1 and 2 hereinabove and Exhibit I. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty day period that began on October 25, 2002, the date the product received permission for marketing and use under Section 505 of the FFDCA, and that will end on December 23, 2002, and in that it contains the information required under 35 U.S.C. §156(d).

(4) As shown by the October 25, 2002 letter from the FDA to MSP Singapore Co., LLC, (attached as Exhibit VIII), the product was subject to a regulatory review period under Section 505 of the FFDCA before its commercial marketing or use.

(5) Finally, ZETIA™ (ezetimibe)Tablets (10mg) were approved by the FDA for the following indications:

Primary hypercholesterolemia – as adjunctive therapy to diet for reduction of elevated total-C, LDL-C and Apo B in patients with primary

(heterozygous familial and non-familial) hypercholesterolemia either alone or with an HMG-Co A reductase inhibitor.

Homozygous familial hypercholesterolemia – in combination with either atorvastatin or simvastatin, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or, if such treatments are unavailable, in combination with either atorvastatin or simvastatin alone; and

Homozygous familial sitosterolemia – as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels.

The permission for the commercial marketing and use of ZETIA™ (ezetimibe) Tablets after regulatory review under Section 505 of the FFDCA is the first permitted commercial marketing and use under Section 505 for humans of the active ingredient, ezetimibe. This is confirmed by the absence of any approved new drug application for the active ingredient in humans prior to October 25, 2002. See Exhibit VIII.

(b) Statement as to length of extension claimed:

The current term of United States Patent No. RE37,721, which issued as U.S. Patent No. 5,767,115 on June 16, 1998 and expires on June 16, 2015, should be extended by 497 days, or to October 25, 2016. This extension was determined on the following basis. As set forth in 35 U.S.C. §156(g)(1), the regulatory review period for ZETIA™ (ezetimibe) Tablets equals the sum of the following two time periods: (1) the period of time beginning on the effective date of IND # 52,791 of May 23, 1997 and ending with the submission of NDA # 21-445 on December 27, 2001, a period of 1,680 days, and (2) the period of time beginning with the submission of NDA

21-165 on December 27, 2001 and ending with the approval of NDA # 21-445 on October 25, 2002, a period of 303 days. These two periods added together equal 1,983 days.

Pursuant to 35 U.S.C. §156(c), the term of the patent eligible for extension shall be extended only for that portion of the regulatory review period which occurs after the date the patent is issued. In this case, this limitation under the introduction to Section 156(c) does apply in that the issue date of U.S. Patent No. 5,767,115 is June 16, 1998 which is after May 23, 1997, the date on which the regulatory review period began. Thus, section 156(c) requires the regulatory review period calculated under 35 U.S.C. §156(g)(1)(B)(i) to be reduced by 389 days to 1,290.

Section 156(c)(2) requires the period calculated under 35 U.S.C. §156(g)(1)(B)(i) (i.e., the period beginning on the effective date of IND # 52,791 and ending with the submission of NDA # 21-445) to be reduced by one-half of the 1,290 day period; this reduction results in a period of 645 days.

From the foregoing calculation, an extension of 948 days results, i.e., the period under 35 U.S.C. §156(g)(1)(B)(i) (645 days) plus the period under 35 U.S.C. §156(g)(1)(B)(ii) (303 days). This extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted. Since the calculated extension (948 days) is less than five years (1,827 days), the limitation under 35 U.S.C. §156(g)(6)(A) does not apply.

Second, under 35 U.S.C. §156(c)(3), if the period remaining in the term of the patent after the date of FDA approval (that is, October 25, 2002 to June 16, 2015), when added to the extension period calculated above would exceed 14 years, the period of extension is to be limited so that the total period (from the FDA approval date to the expiration date of the extended patent term) does not exceed 14 years. In this case, the total of the remaining term of the patent after the date of approval -- i.e., from October 25, 2002 to June 16, 2015, or 4,617 days, which when added to the extension period calculated above of 948 days equals 5,565 days -- is greater than the 14 year (5,114 days) limit. As a result, the patent term extension of 948 days is reduced under 35 U.S.C. §156(c)(3) to 497 days.

Accordingly, U.S. Patent No. RE37,721 is eligible for an extension of 497 days, from June 16, 2015 to October 25, 2016.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE SEC. 1.765):

Schering acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (SEE SEC. 1.20(J)):

The Commissioner is authorized to charge our Deposit Account No. 19-0365 in the amount of **$1,120.00** or any other fee necessary for this application to prevent it from becoming inadvertently abandoned.

(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:

Thomas D. Hoffman
Schering Corporation
Patent Department
K-6-1 1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone No. (908) 298-5037
Facsimile No. (908) 298-5388

* * *

I, THOMAS D. HOFFMAN, Registration No. 28,221, as duly appointed attorney (by virtue of the Power of Attorney duly executed by James R. Nelson, Vice President for Schering Corporation) for Applicant, Schering Corporation, the owner of record of U.S. Patent No. RE37,721 (by virtue of the aforesaid assignment, see Exhibit I), submit this application for an extension of the term of this patent and declare that:

(i) I am authorized to practice before the United States Patent and Trademark Office;

(ii) I have reviewed and understand the contents of the attached application for extension of patent term of U.S. Patent No. RE37,721;

(iii) I believe that the patent is subject to extension under 35 U.S.C. §156 and 37 C.F.R. §§1.710 - 1.791.

(iv) I believe that the length of extension claimed in this application is fully justified pursuant to 35 U.S.C. §156 and the applicable regulations; and

(v) I believe that the patent for which an extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. §156 and 37 C.F.R. §1.720.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. RE37,721.

Date: 12/12/2002

By: Thomas D. Hoffman

Thomas D. Hoffman
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